REMARKS

Introductory Comments:

Claims 1-4, 10, 11, 15, 16, 20, 21 and 27-31 were examined in the Office Action under reply and stand variously rejected under (1) 35 U.S.C. §112, first paragraph (claims 1, 10, 11 and 27-29); (2) 35 U.S.C. §101 (claims 28-31); (3) 35 U.S.C. §102(b) (claims 1-4 and 27-30); and (4) 35 U.S.C. §103(a) (claims 1-4, 10, 11, 15, 16, 20, 21 and 27-31). These rejections are believed to be overcome for reasons discussed below.

Overview of the Above Amendments:

Claims directed to non-elected inventions have been cancelled. Additionally, subject matter from claims 2 and 11 has been incorporated into independent claim 1 and recitations from claim 30 have been incorporated into independent claims 27 and 29. Claims 4, 28 and 31 have been amended to depend from non-cancelled claims.

Support for the above amendments can be found in the original claims as filed, as well as throughout the application. The amendments are made solely to expedite prosecution, for reasons unrelated to patentability, and do not constitute an acknowledgment that the Examiner's position is correct. In view of the foregoing amendments and following remarks, applicants submit that the application is in condition for allowance.

Rejections Under 35 U.S.C. §112, First Paragraph:

Claims 1, 10, 11 and 27-29 were rejected under 35 U.S.C. §112, first paragraph as nonenabled. The Office argues the "claims read on a method for generating any cell line comprising any kind of dominant negative disabling mutation for any host cellular housekeeping genes and gene products that are used by the virus in replication cycle" and that the claims read on "any sub-genomic replicon." Office Action, page 3. Applicants believe the claims to be adequately enabled. Nevertheless, the substance of claims 2, 12 and 30 has been incorporated into independent claims 1, 27 and 29. Claim 2, reciting that the anti-virus response factor is PKR activity, and claims 12 and 30, reciting that the sub-genomic viral replicon is an HCV sub-genomic replicon, were not subject to this

rejection. Thus, the rejection of claims 1, 10, 11 and 27-29 under 35 U.S.C. §112, first paragraph has been overcome and withdrawal thereof is respectfully requested.

Rejection Under 35 U.S.C. §101:

Claims 28-31 were rejected as "directed to non-statutory subject matter" for allegedly reading on "naturally occurring materials." Office Action, page 5. Applicants respectfully disagree. In particular, all of the rejected claims include the presence of an HCV sub-genomic replicon. As explained in the specification at page 5, lines 9-12, a sub-genomic viral replicon contains less than the full complement of genes and other features of the viral genome. Additionally, all of these claims pertain to cells with disabled PKR activity. Thus, contrary to the Office's assertions, the claims do not read on nature and withdrawal of this basis for rejection is respectfully requested.

Rejection Under 35 U.S.C. §102:

Claims 1-4 and 27-30 were rejected under 35 U.S.C. §102(b) as anticipated by Terenzi et al., *Nuc. Acids Res.* (1999) 27:4369-4375 ("Terenzi"). Applicants note that claim 12, directed to methods where the sub-genomic viral replicon is an HCV sub-genomic replicon, is free of the art. Claim 1 has been amended to incorporate the recitations from claim 12, thus the rejection of claims 1-4 has been overcome.

Similarly, independent claims 27 and 29 have been amended to incorporate recitations from claim 30, and therefore recite that the sub-genomic viral replicon is an HCV sub-genomic replicon. Applicants submit that the rejection of claim 30 under 35 U.S.C. §102(b), over Terenzi, is in error. In particular, Terenzi's cells are transfected with a plasmid that contains a Semliki Forest Virus replicon. Terenzi nowhere describes a PKR-disabled cell that includes an HCV sub-genomic viral replicon. In fact, the Examiner acknowledges such is the case at page 6 of the Office Action.

The law is clear that in order to anticipate a claim, a single source must contain all of the elements of the claim. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 90 (Fed. Cir. 1986). *Atlas Powder Co. v. E. I. du Pont De Nemours & Co.*, 224 USPQ 409, 411 (Fed. Cir. 1984). Moreover, the single source must disclose all of the claimed elements "arranged as in the claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ 2d 1913, 1920 (Fed. Cir. 1989); *Connell v. Sears Roebuck & Co.*, 220 USPQ 193, 198

(Fed. Cir. 1983). Finally, the law requires identity between the claimed invention and the prior art disclosure. *Kalman v. Kimberly-Clar Corp.* 218 USPQ 2d 781, 789 (Fed. Cir. 1983, cert. denied, 465 U.S. 1026 (1984)).

Since Terenzi fails to describe each and every element of applicants' claims, namely, a PKR-disabled cell with an HCV sub-genomic replicon, Terenzi cannot anticipate the present invention. Thus, withdrawal of the above basis for rejection under 35 U.S.C. §102(b) is respectfully requested.

Rejections Under 35 U.S.C. §103:

Claims 1-4, 10, 11, 15, 16, 20, 21 and 27-31 were rejected under 35 U.S.C. §103(a) as being unpatentable over Terenzi in view of Lohmann et al., *Science* (1999) 285:110-113 ("Lohmann"). The Office argues Terenzi teaches cell lines transformed with dominant negative mutated PKR transfected with a plasmid or viral vector that contains a Semliki Forest Virus replicon. The Office correctly recognizes that Terenzi does not teach using the cell line to support an HCV replicon. Lohmann is cited for teaching an HCV sub-genomic replication system in a Hu-7 cell to express HCV gene products. The Examiner notes that the efficiency of protein expression by the HCV sub-genomic replicon in Lohmann's system is limited. The Office concludes that one of skill in the art would therefore have been motivated to combine the methods of Terenzi and Lohmann to establish an efficient HCV sub-genomic replication system. Office Action, page 6. However, applicants respectfully disagree with this assessment.

It is well settled that for purposes of 35 U.S.C. §103, the differences between the prior art and the claims are not determined based on whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. MPEP §2141.02 citing *Stratoflex, Inc. v. Seroquip Corp.*, 218 USPQ 871 (Fed. Cir. 1983) and *Schenck v. Northon Corp.*, 218 USPQ 698 (Fed. Cir. 1983) (emphasis in the original). Additionally, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found in either the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941 (Fed. Cir. 1992). Further, the fact that references can be combined or modified or that the claimed

invention is well within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish *prima facie* obviousness. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); *Ex parte Levengood*, 28 USPQ2d 1300 (BPAI 1993).

Applicants respectfully submit the invention as a whole is not obvious and there is no suggestion to combine the teachings of the art as asserted. In particular, Lohmann pertains to the replication of sub-genomic HCV RNAs in a hepatoma cell line. Despite the Examiner's assessment, the replicons were found to replicate to high levels (page 112, col. 2), albeit at levels lower than pestivirus replicons (page 112, col. 3), and expression of HCV antigens was detected in cells (see Fig. 3). Although, Lohmann obtained only a few cell clones that stably replicated sub-genomic HCV RNAs, Lohmann fails to teach or suggest any method involving disabling PKR activity to make the cellular environment more favorable to replication of sub-genomic HCV replicons. Rather, Lohmann teaches the use of a neomycin (G418) resistance marker in HCV subgenomic replicons to overcome problems caused by a selective "loss or growth disadvantage of cells supporting virus replication" (page 110, col. 2). Lohmann concludes on page 112 that "the low number of cell clones obtained may indicate that only a few cells in the culture support HCV RNA replication, or that a level of replication required for G418 resistance was reached in only a few cells." Such a conclusion would motivate one to search for the "conditions or factors" present in the few cells that permit replication, not to eliminate PKR activity. Nowhere does Lohmann mention disabling any host anti-viral response factors, let alone PKR; therefore, Lohmann cannot provide the requisite motivation to disable PKR activity, as recited in the claims.

Moreover, the fact that Terenzi's system might provide a more desirable result is simply not enough to support the stated obviousness rejection. In making the present rejection, it appears the Office is applying an impermissible "obvious to try" standard which is not a proper basis for a rejection under 35 U.S.C. §103. See, e.g., *In re Dow Chemical*, 5 USPQ2d 1529 (Fed. Cir. 1988); *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988). As explained in *In re Deuel*, 34 USPQ2d 1210, 1217 (Fed. Cir. 1995): "A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out."

Thus, applicants submit there is no suggestion or incentive to combine Terenzi with Lohmann. Without a suggestion to modify the references evident in the prior art,

the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). See, also, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

Based on the foregoing, applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103.

CONCLUSION

Applicants respectfully submit that the claims define a patentable invention. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

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